REMARKS/ARGUMENTS

Claims 119-123 remain pending in this application. Applicants respectfully traverse the present rejections.

Claim Rejections – 35 U.S.C. §101

Claims 119-123 stand rejected under 35 U.S.C. §101 because, allegedly, "the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility."

The Examiner maintains that "the instant application does not disclose a specific biological role for this protein or the antibody that binds to this protein or their significance to a particular disease, disorder or physiological process, which one would wish to manipulate for a desired clinical effect (page 2-3, last line onwards of non-final Office action). The Examiner cites new reference Anderson *et al.* to show that allegedly, strong opposing evidence exists on the topic of predicting protein expression from corresponding mRNA levels. Applicants respectfully traverse this rejection.

Arguments

Applicants maintain that the specification, as filed, provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO830 polypeptide of SEQ ID NO:175 and that the increase in gene amplification for the DNA encoding PRO830 is sufficient to confer patentable utility to the instantly claimed PRO830 polypeptides and antibodies binding thereto.

As discussed previously, it is not a legal requirement to establish a "necessary" correlation between an increase in gene copy number and protein expression levels or to find evidence that protein levels can be accurately predicted from gene amplification data. Instead, as discussed before, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, the question is rather if it is more likely than not that a person of ordinary skill in the pertinent art

would recognize such a positive correlation between gene amplification levels and protein levels. Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Anderson *et al.*

The Examiner cited the reference Anderson *et al.* in support of the position that "there is a poor correlation (0.48) between mRNA and protein levels in liver cells" (Page 5 of the instant Office Action).

Applicants respectfully disagree and submit that, as pointed out in the Anderson *et al.* reference itself, a correlation coefficient of 0.48 is "close to the middle position between a perfect correlation (1.0) and no correlation whatsoever (0.0)" (Anderson *et al.*, page 536). Therefore, far from being a "poor" correlation, such a coefficient would obviously be considered significant in the art.

Furthermore, the authors of Anderson *et al.* themselves admit to several experimental flaws that severely limit the accuracy of the data presented in their study. For example, their protein measurements relied on CBB (Coumassie blue) binding, which is well-known to bind different proteins with different affinities. It is also known, in the art, that Coomassie dye stain is a very insensitive method of measuring protein. More significantly, however, the authors did not measure actual mRNA abundance for each protein, but looked at the numbers of clones found in a library. The precision of these measurements is limited because several proteins studied were represented only by one or two clones. As Anderson *et al.* state, "such small numbers of clones lead to potentially large quantitative errors because of sampling error" (page 536, col. 1). This is clearly illustrated in Table 1, where the protein data, from proteins represented by merely one or two clones, strongly affected the non-linearity of the total dataset. Obviously, such technical limitations affect the accuracy of the mRNA: protein abundance data as well, and their conclusions. Finally, even assuming it is accurate, the conclusion by Anderson *et al.* does not support the Examiner's position. To the contrary, the data in Anderson *et al.* suggest that there is a significant correlation between mRNA and protein levels. Anderson *et al.* have observed a correlation coefficient of 0.48 between protein and mRNA abundance. As shown, for example, in Chen *et al.*, (cited by Examiner in previous Office action dated November 25, 2005 and

discussed in detail in response of February 27, 2006) correlation coefficients over 0.25 are deemed to be significant (see Table II, and page 309, col. 1). In fact, the highest correlation coefficient reported by Chen *et al.* is 0.4003, less than the 0.48 observed for the Anderson *et al.* data. Accordingly, the Applicant respectfully submits that the Examiner cannot rely on the teachings of Anderson *et al.* to establish a *prima facie* showing of lack of utility.

Besides Applicants have previously acknowledged the correlation between changes in DNA levels and protein levels is not exact, and there are exceptions (*see, e.g.,* abstracts attached as Exhibit 21 in previously filed IDS of 17 August, 2006). But correspondingly, there are other articles that support that there is correlation between mRNA and protein abundance. For example, articles by Haynes *et al.* , Orntoft *et al.*, Futcher *et al.* support the Applicants position. The article by Futcher *et al.* (Mol. Cell Biol. 1999; 19(11):7357-68) (abstract as Exhibit 13 of previously submitted IDS) the authors conducted a study of mRNA and protein expression in yeast. Futcher *et al.* report "a good correlation between protein abundance, mRNA abundance, and codon bias." *Id.* at Abstract. Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in DNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility.

Applicants maintain that, both Polakis Declarations (Polakis I and II) and the teachings in the art, represented by the 148 references presented in the IDS of 17 August, 2006, support Applicants' assertion, in general, that changes in mRNA level generally lead to corresponding changes in the level of the expressed protein. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

Therefore, Applicants request that the Examiner reconsider this rejection and maintain that they have demonstrated utility for the PRO830 polypeptide and antibodies that bind thereto. Applicants add that the gene amplification data clearly supports a role for PRO830 and antibodies as a lung tumor marker. Accordingly, the present 35 U.S.C. §101 utility rejections should be withdrawn.

Claim Rejections – 35 U.S.C. §112, First Paragraph

Claims 119-123 stand further rejected under 35 U.S.C. §112, first paragraph, since allegedly "the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, one skilled in the art clearly would not know how to use the claimed invention."

For the reasons outlined above, Applicants maintain that one skilled in the art would know how to make and use the instant invention (PRO830 antibodies), based on the disclosures in the specification and the knowledge in the art, and use it as a lung tumor marker. Accordingly, the present rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39780-2730P1C10**). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: December 7, 2006

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